REMARKS

Applicants respectfully request reconsideration and allowance of the present application.

I. CLAIM STATUS

Applicants have amended claims 12 and 16, without prejudice or disclaimer, to present the claimed invention in a clearer manner and to advance the prosecution. Applicants reserve the right to file one or more continuing applications directed to the subject matter omitted by the present amendment. Support for the amended claims may be found throughout the specification as filed and, in particular, for amended claim 12 in original claim 2, page 5, line 7, through page 6, line 15. No new matter has been added.

Applicants have canceled claims 13-15 and 17. Applicants reserve the right to file one or more continuing applications directed to the canceled subject matter.

Applicants have added new claims 23-28. Support for new claims may be found throughout the specification as filed and, in particular, on pages 18-19 and Table 1. No new matter has been added.

After the amendment, pending claims include a) examined claims 12, 16, and 18-22 and b) new claims 23-28.

II. CLAIM REJECTION UNDER 35 U.S.C. § 112, ¶ 1

Claims 12-16 and 18-22 stand rejected because, according to the PTO, the specification, while being enabling for the treatment of depression with the administration of a compound of formula I, does not reasonably provide enablement for the prevention of depression. Applicants disagree with the rejection and reserve the right to address the rejection in one or more continuing applications. At the same time, Applicants submit that the revised claim set obviates the rejection because it does not recite the prevention of depression. Accordingly, Applicants request withdrawal of the rejection.

III. CLAIM REJECTION UNDER 35 U.S.C. § 102(b)

Claims 12 and 18-22 stand rejected as anticipated by Aktogu et al. (U.S. patent no. 5,034,396). Applicants respectfully traverse.

Aktogu does not teach at least one element of the claimed invention.

For example, Aktogu does not teach treating a treatment resistant depression (TRD) by administering to a subject in need thereof a pharmaceutical composition comprising a compound with formula (I) or its pharmaceutically acceptable salt as amended claim 12 recites. Aktogu relates to a method of treating depression with optically active isomers of 20,21-dinoreburnamenines. In his disclosure, Aktogu only uses a generic term "depression" and does not specify particular types of depression for which optically active isomers of 20,21-dinoreburnamenines may be useful.

Applicants respectfully submit that TRD recited in the pending claims is one of the forms of a Major Depressive Disorder (MDD), which in turn is one of the subtypes of depressions listed in "Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition" (DSM-IV), which is a reference book for mental disorders produced by the American Psychiatric Association, see e.g. specification as filed pages 1-6 and, in particular, page 1, lines 18-23, page 4, lines 4-7, page 5, lines 3-6. Subtypes of depression, other than MDD, include dysthymic disorder, reactive depression, exhaustion depression, depression due to physiological particularities (child, pregnancy or elderly depression) and seasonal affective disorder.

Applicants respectfully submit that one of ordinary skill in the art would not envision based on Aktogu's use of the generic term "depression" that optically active isomers of 20,21-dinoreburnamenines could be useful for treating each and every category of depression, such as MDD, and each and every form of each category of depression, such as TRD.

In sum, because Aktogu does not teach all the elements of claim 12, Applicants request withdrawal of the rejection.

For the record, the PTO itself acknowledged that Aktogu does not teach treatment of a treatment resistant depression by not rejecting examined claim 13 as anticipated by Aktogu and by stating on page 5 of the Office Action that "Aktogu does not expressly teach that the subject is partially or totally resistant to classical antidepressants."

Applicants respectfully submit that "depression in a subject partially or totally resistant to classical antidepressants" is by definition a treatment resistant depression, see page 5, lines 2-6.

IV. CLAIM REJECTION UNDER 35 U.S.C. § 103(a)

Claims 13-16 stand rejected as obvious over Aktogu et al. (U.S. patent no. 5,034,396) in view of Pickar et al. (U.S. patent no. 5,663,167). Applicants respectfully traverse.

Because amended claim 12 relates to treating a treatment resistant depression, i.e. a depression in a subject partially or totally resistant to classical antidepressants, Applicants provide their comments traversing the PTO's rejection as applied to examined claims 13 and 16 only. Applicants reserve the right to address the PTO's comments as applied to rejected claims 14 and 15 in one or more continuing applications.

The PTO acknowledges the following deficiencies of Aktogu as related to examined claims 13 and 16: "Aktogu does not expressly teach that the subject is partially or totally resistant to classical antidepressants." To remedy the admitted deficiencies of Aktogu as related to examined claims 13 and 16: the PTO relies on Pickar as follows on page 6 of the Office Action:

> Pickar teaches that the addition of an alpha$_2$ receptor antagonist are useful in the treatment of patents suffering from serious psychotic mental illness who have proven resistant to treatments with known antipsychotic neuroleptics alone (column 2, lines 40-43).

Based on such interpretation of Pickar, the PTO makes the following conclusions as related to examined claim 13 in the paragraph bridging pages 6-7 of the Office Action:

> It would have been obvious to one of ordinary skills in the art to employ the administration of formula I which is (30, 14β) 14, 15-dihydro 20,21-

dinoreburnamenin-14-ol and (14β,16α) 14, 15-dihydro 20, 21-dinoreburnamenin-14-ol to a subject [that] is partially or totally resistant to classical anti-depressants. One would have been motivated to treat a subject is partially or totally resistant to classical anti-depressants because Pickar teaches that alpha$_2$ receptor antagonist are useful in the treatment of mental illness (e.g. bipolar, schizophrenia) to subjects who are drug resistant to known antipsychotic neuroleptics alone. It would have been obvious to one of ordinary skills to employ alpha$_2$ receptor antagonist in combination or singularly with known antidepressants since it is taught in the prior art that alpha$_2$ receptor antagonist are useful in the treatment of drug resistant subject with a reasonable expectation of success.

Applicants respectfully submit that the PTO failed to establish a *prima facie* case of obviousness because the PTO failed to make its obviousness analysis explicit. In this regard, Applicants respectfully bring the PTO's attention to the legal standard for obviousness rejections set forth in *KSR International Co. v. Teleflex Inc.*, 550 U.S._, 82 USPQ2d 1385 (2007), where the Supreme Court emphasized that the analysis supporting a rejection under 35 U.S.C. §103(a) should be made explicit. The Supreme Court also stated, quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), that "'[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning the legal conclusion of obviousness.'"

Applicants respectfully submit that the PTO's assertion in the last sentence in the paragraph bridging pages 6-7 of the Office Action regarding "a reasonable expectation of success" is conclusory statement, which is not permissible in an obviousness analysis. Applicants respectfully submit that one ordinary skill in the art would **not** have had a reasonable expectation of success for treating a treatment resistant depression based on Aktogu and Pickar, which do not provide any evidence related to treatment of the treatment resistant depression, at least because currently, there is no medicament available for treating such condition.

In sum, because the PTO failed to establish a *prima facie* case of obviousness, Applicants request withdrawal of the rejection.

V. ADDITIONAL COMMENTS

As the specification as filed explains on page 5, 30-46% of depressive patients display a partial or total resistance to classical antidepressant treatment, i.e. suffer from TRD. Even in the case of only partial resistance, TRD leads to increasingly close relapses and finally to total resistance, even in relatively young people. Thus, a need exists for finding an effective treatment against TRD.

Currently, there is no medicament available for TRD, the only available treatments are experimental physical treatments aiming at stimulating the brain of TRD patients. These treatments include:

ElectroConvulsive Therapy (ECT): electrodes are placed on the brain and, under general anaesthesia, electricity is sent through the brain to provoke convulsions (see enclosed Lancet UK ECT Review Group (2003). Lancet 361, 799-808);

Transcranial Magnetic Stimulation (TMS): the principle is the same as ECT, unless the stimulation is electromagnetic and not electric (see enclosed Couturier JL et al., J. Psychiatry Neurosci., 2005 Mar;30(2):83-90);

Vagus Nerve Stimulation (VNS): a pulse generator and a nerve stimulator electrode is surgically placed in a pocket formed under the skin, below the left collarbone, to stimulate the left vagus nerve (see enclosed Sackeim, H.A et al. (2001) Neuropsychopharmacology, 25, 713–728), and

Deep Brain Stimulation (DBS): electrodes are implanted in the brain within a particular brain region to stimulate this particular region (see enclosed Mayberg, H.S. et al. (2005) Neuron, 45, 651–660).

The efficacy of these physical treatments is not yet clearly established for TRD patients, and secondary effects are yet to be properly measured. In addition, even if not all these treatments are as invasive as DBS, all of them imply the intervention of a medical practitioner.

Several research teams have demonstrated a hypoactivity of the prefrontal cortex in TRD patients. In addition, a reactivation of this brain region is correlated with a good

response to treatment. Thus, all of the above described physical therapies aim at stimulating the hypoactive prefrontal cortex.

The present Applicants surprisingly discovered that the same effect, i.e. stimulating the hypoactive prefrontal cortex, can be obtained via non-invasive therapy using the 14,15-dihydro-20,21-dinoreburnamenin-14-ol derived compounds. Indeed, the results displayed in Table 1 of the specification as filed show that the treatment of Balb/c mice with 14,15-dihydro-20,21-dinoreburnamenin-14-ol derived compounds leads to the following unexpected effects:

1. an increase of the number of noradrenergic neurons in the locus caerelus, which is a fundamental brain modulator system correlated with the prefrontal cortex,
2. an increase of the number of hypocretin neurons in the hypothalamus, these neurons being able to activate the noradrenergic neurons of the locus caerelus,
3. a concomitant increase in the density of noradrenalin fibers in the prefrontal cortex, which has been shown to be the brain region that needs to be reactivated to escape treatment resistance, and
4. the capacity to reactivate the capacity of Balb/c mice to display increased REM sleep after sleep deprivation, which demonstrates the efficient activity of the prefrontal cortex.

These surprising results 1-4 show that, by restoring a complex brain circuitry, the 14,15-dihydro-20,21-dinoreburnamenin-14-ol derived compounds are able to reactivate the brain region, for which hypoactivity is associated with TRD.

Applicants respectfully submit that new claims 23-28 recite one or more of the surprising results 1-4. Thus, claims 23-28 are non-obvious over Aktogu and Pickar because one of ordinary skill in the art would have arrived at the effects recited in claims 23-28 based on Aktogu and Pickar.

CONCLUSION

Applicants believe that the present application is in condition for allowance. Favorable consideration of the application is respectfully requested. The Examiner is invited

to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith,

Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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